Mechanisms of action of hESC-secreted proteins that enhance human and mouse myogenesis

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Public Summary:
Abstract: Adult stem cells grow poorly in vitro compared to embryonic stem cells, and in vivo stem cell maintenance and proliferation by tissue niches progressively deteriorates with age. We previously reported that factors produced by human embryonic stem cells (hESCs) support a robust regenerative capacity for adult and old mouse muscle stem/progenitor cells. Here we extend these findings to human muscle progenitors and investigate underlying molecular mechanisms. Our results demonstrate that hESC-conditioned medium enhanced the proliferation of mouse and human muscle progenitors. Furthermore, hESC-produced factors activated MAPK and Notch signaling in human myogenic progenitors, and Delta/Notch-1 activation was dependent on MAPK/pERK. The Wnt, TGF-β and BMP/pSmad1,5,8 pathways were unresponsive to hESC-produced factors, but BMP signaling was dependent on intact MAPK/pERK. c-Myc, p57, and p18 were key effectors of the enhanced myogenesis promoted by the hECS factors. To define some of the active ingredients of the hESC-secretome which may have therapeutic potential, a comparative proteomic antibody array analysis was performed and identified several putative proteins, including FGF2, 6 and 19 which as ligands for MAPK signaling, were investigated in more detail. These studies emphasize that a “youthful” signaling of multiple signaling pathways is responsible for the pro-regenerative activity of the hESC factors.

Scientific Abstract:
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